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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
09/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,022	BJORQUIST ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *2-4,7-15 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,16,17 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/2006 and 3/6/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restriction filed on June 12, 2008 is acknowledged. Claims 1-22 are pending in this application.

Restriction

1. Applicant's election without traverse of Group I (claims 1, 5-6, 16-17 and 22), and the species of Compound 1 in the reply filed on June 12, 2008 is acknowledged.

2. The restriction requirement is deemed proper and is made FINAL in this office action. Claims 2-4, 7-15 and 18-21 are withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 5-6, 16-17 and 22 are examined on the merits in this office action.

Objection-Minor Informalities

3. The title is objected to because the title is too long. The title is limited to 2-7 words maximum (see MPEP 601). A new title is required that is clearly indicative of the invention to which the claims are directed.

4. Claims 16-17 are objected to for the following reason: Claims 16 and 17 are dependent on claim 2, which is drawn to nonelected invention. Applicant is advised to rewrite the claims into independent claims.

5. Claim 1 is objected to for the following reason: Claim 1 recites, "…wherein inhibition of carboxypepsidase U is beneficial…" There appears to be a spelling error. The word "carboxypepsidase" should be corrected to "carboxypeptidase".

Rejection-35 U.S.C. 112, 1st

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 5-6, 16-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of diseases involved in carboxypeptidase U (CPU), does not reasonably provide enablement for prophylaxis of diseases involved with carboxypeptidase U. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are

weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to method for treatment or prophylaxis of a disorder, condition or disease associated with Carboxypeptidase U (CPU) comprising administering a therapeutically effective amount of a compound of formula (I) to a warm-blooded animal in need thereof. The specification does not define what and effective amount is.

(2) The state of the prior art:

The Merck manual indicates that there are plethora of disorders known that are related to thrombosis, for example, arterial, cardiac, cavernous sinus, cerebral, coronary artery, deep venous and others (see Merck manual, "thrombosis index entries"). Merck manual indicates that numerous genetic acquired, and environmental factors can tip the balance in favor of coagulation, leading to the pathologic formation of thrombi in veins (e.g., deep vein thrombosis [DVT]), arteries (e.g., MI, ischemic stroke), or cardiac chambers. Thrombi can obstruct blood flow at the site of formation or detach and embolize to block a distant blood vessel (e.g., pulmonary embolism, stroke) (see Merck manual, "Thrombotic Disorders", 1st paragraph). Further, Merck manual indicates that genetic defects increase the propensity for venous thromboembolism. However, other disorders and environmental factors can increase the risk of thrombosis, especially if

present in conjunction with one of the genetic abnormalities. Stasis associated with surgery or orthopedic or paralytic immobilization; heart failure; pregnancy; and obesity increase the risk of venous thrombosis. Tissue injury from trauma or surgery exposes tissue factors to blood and increases the risk of venous thrombosis. Neoplastic cells predispose to venous thrombosis. Sepsis and other severe infections associated with increased tissue factor exposure can increase the risk of venous thrombosis. Oral contraceptives that contain estrogen increase the risk of arterial and venous thromboembolism. Atherosclerosis predispose to arterial thrombi (see Merck manual, “Thrombotic Disorders", 2nd to 8th paragraphs). Merck manual indicates that for diagnosis and treatment, predisposing factors should always be considered. In some cases, the condition is clinically obvious. If no predisposing factor is readily apparent, further evaluation should be conducted in patients with a family history of venous thrombosis (see Merck manual, "Thrombotic Disorders", 9th paragraph). The Merck manual further indicates diagnostic tests for the cause of thrombosis (see Merck manual, “Thrombotic Disorders”, 10th to 18th paragraphs).

The Merck manual indicates that Atherosclerosis is patchy intimal plaques (atheromas) in medium-sized and large arteries; the plaques contain lipids, inflammatory cells, smooth muscle cells, and connective tissue. The Merck manual indicates that the risk factors include dyslipidemia, diabetes, cigarette smoking, family history, sedentary lifestyle, obesity, and hypertension. Diagnosis is clinical and confirmed by angiography, ultrasonograpy, or other imaging tests. Treatments include risk factor and dietary modification, physical activity, antiplatelet drugs, and

antiatherogenic drugs (see Merck manual, “Atherosclerosis”, 1st paragraph). The Merck manual indicates that atherosclerotic plaques may be stable or unstable. Stable plaques regress, remain static, or grow slowly over several decades until they may cause stenosis or occlusion. Unstable plaques are vulnerable to spontaneous erosion, fissure, or rupture, causing acute thrombosis, occlusion, and infarction long before they cause stenosis. The Merck manual indicates that most clinical events result from unstable plaques, which do not appear severe on angiography (see Merck manual, "Atherosclerosis", 6th paragraph). The Merck manual indicates that there are multiple risk factors (see Merck manual, “Atherosclerosis”, “Risk Factors”). Furthermore, the Merck manual indicates that atherosclerosis is initially asymptomatic, often for decades. Symptoms and signs develop when lesions impede blood flow. Atherosclerosis may also cause sudden death without preceding stable or unstable angina pectoris (see Merck manual, “Atherosclerosis”, “Symptoms and Signs”). Additionally, the Merck manual indicates that diagnosis depends on the presence of absence of symptoms (see Merck manual, "Atherosclerosis", "Diagnosis"). Furthermore, the Merck manual indicates different treatments, such as lifestyle change, drug treatment of diagnosed risk factors, antiplatelet drugs, or possibly statins, ACE inhibitors, β-blockers, and diet changes.

The art recognizes that there are countless different conditions, disorders and diseases that are associated with thrombosis, for example, arterial, cardiac, cavernous sinus, cerebral, coronary artery, deep venous and others, and atherosclerosis, but does not provide how to determine the individuals who are susceptible to these disorders,

condition or diseases. The Merck manual also indicates types of treatment of these disorders. Several dictionaries define "prophylaxis" as "the prevention of disease" (Dictionary.com), "prevention of or protective treatment for disease" (American Heritage Dictionary) (see enclosed definitions). The Merck manual recognizes different types of treatment of diseases, such as thrombosis or atherosclerosis, but does not provide how to determine the individuals or how to prevent the diseases or disorders from occurring in all individuals.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determination of predicting those who are susceptible to disorders, conditions and diseases that are related to carboxypeptidase U (CPU). Since the activity is based on determining the patient population that is susceptible to disorders, conditions and diseases, the predictability in the art is low. This is due to the fact that the art has recognized that there are plethora of different conditions, disorders and diseases, but does not provide how to determine the individuals who are susceptible to these disorder, condition or disease such as atherosclerosis and thrombosis. Additionally, not everyone suffers from thrombosis or atherosclerosis.

As described above, the Merck manual indicates that there are plethora of disorders known that are related to thrombosis, for example, arterial, cardiac, cavernous sinus, cerebral, coronary artery, deep venous and others (see Merck manual, "index entries"). Merck manual indicates that numerous genetic acquired, and environmental factors can tip the balance in favor of coagulation, leading to the pathologic formation of thrombi in veins (e.g., deep vein thrombosis [DVT]), arteries (e.g., MI, ischemic stroke), or cardiac chambers. Thrombi can obstruct blood flow at the site of formation or detach and embolize to block a distant blood vessel (e.g., pulmonary embolism, stroke) (see Merck manual, “Thrombotic Disorders”, 1st paragraph). Further, Merck manual indicates that genetic defects increase the propensity for venous thromboembolism. However, other disorders and environmental factors can increase the risk of thrombosis, especially if present in conjunction with one of the genetic abnormalities. Stasis associated with surgery or orthopedic or paralytic immobilization; heart failure; pregnancy; and obesity increase the risk of venous thrombosis. Tissue injury from trauma or surgery exposes tissue factors to blood and increases the risk of venous thrombosis. Neoplastic cells predispose to venous thrombosis. Sepsis and other severe infections associated with increased tissue factor exposure can increase the risk of venous thrombosis. Oral contraceptives that contain estrogen increase the risk of arterial and venous thromboembolism. Atherosclerosis predispose to arterial thrombi (see Merck manual, “Thrombotic Disorders", 2nd to 8th paragraphs). Merck manual indicates that for diagnosis and treatment, predisposing factors should always be considered. In some cases, the condition is clinically obvious. If no predisposing factor

is readily apparent, further evaluation should be conducted in patients with a family history of venous thrombosis (see Merck manual, "Thrombotic Disorders", 9th paragraph). The Merck manual further indicates diagnostic tests for the cause of thrombosis (see Merck manual, “Thrombotic Disorders”, 10th to 18th paragraphs). The Merck manual indicates that Atherosclerosis is patchy intimal plaques (atheromas) in medium-sized and large arteries; the plaques contain lipids, inflammatory cells, smooth muscle cells, and connective tissue. The Merck manual indicates that the risk factors include dyslipidemia, diabetes, cigarette smoking, family history, sedentary lifestyle, obesity, and hypertension. Diagnosis is clinical and confirmed by angiography, ultrasonograpy, or other imaging tests. Treatments include risk factor and dietary modification, physical activity, antiplatelet drugs, and antiatherogenic drugs (see Merck manual, “Atherosclerosis”, 1st paragraph). The Merck manual indicates that atherosclerotic plaques may be stable or unstable. Stable plaques regress, remain static, or grow slowly over several decades until they may cause stenosis or occlusion. Unstable plaques are vulnerable to spontaneous erosion, fissure, or rupture, causing acute thrombosis, occlusion, and infarction long before they cause stenosis. The Merck manual indicates that most clinical events result from unstable plaques, which do not appear severe on angiography (see Merck manual, "Atherosclerosis", 6th paragraph). The Merck manual indicates that there are multiple risk factors (see Merck manual, “Atherosclerosis”, “Risk Factors”). Furthermore, the Merck manual indicates that atherosclerosis is initially asymptomatic, often for decades. Symptoms and signs develop when lesions impede blood flow. Atherosclerosis may also cause sudden death

without preceding stable or unstable angina pectoris (see Merck manual, “Atherosclerosis”, “Symptoms and Signs”). Additionally, the Merck manual indicates that diagnosis depends on the presence of absence of symptoms (see Merck manual, "Atherosclerosis", "Diagnosis"). Furthermore, the Merck manual indicates different treatments, such as lifestyle change, drug treatment of diagnosed risk factors, antiplatelet drugs, or possibly statins, ACE inhibitors, β-blockers, and diet changes.

The claims don’t identify the patient population, therefore, the claim implies that anyone can be protected against any disorder, condition or disease wherein inhibition of carboxypeptidase U (CPU) is beneficial. However, the Applicant has not shown who will be susceptible to disorder, condition or disease and the types of disorder, condition or disease. There are too many variables between the patient populations, thus, it clearly shows the unpredictability of the art.

(5) The breadth of the claims:

The claim is drawn to a method of treatment or prophylaxis of disease or medical condition wherein inhibition of carboxypeptidase U is beneficial, the method comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound of formula (I).

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The specification describes the isolation of Compounds 1 to 10 from the *sponge Melophlus* species (see Example 1). Example 2 of the instant specification describes the isolation of Compound 11 from sponge samples of *Candidaspongia flabellate* (see Example 2). Examples 3-4 describe the synthesis of Compounds 1 and 13-16 (see Examples 3-4). Example 5 describes IC_{50} values of Compounds 2, 8 and 12 on substrate concentration of 4 mM (see Example 5 and Table I). The specification discloses that the Hendriks et al reference (Clinical Chemistry, 1985, 31: 1936-1939) were followed to get the activities of some of the Compounds. The Hendriks reference is based on carboxypeptidase N activity. Although the specification provides guidance on how to make the compounds, the specification does not provide guidance on how to administer the compound and the effective dosage, it is unclear as to when to administer the compound and the patient population. The instant specification discloses that the Inhibitors of carboxypeptidase U are expected to facilitate fibrinolysis (see instant paragraph [0003]). 2-mercaptomethyl-3-guanidinoethylthiopropanoic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU (Hendriks et al, Biochimica et Biophysica Acta, 1034 (1990) 86-92) (see paragraph [0004]). Paragraph [0008] lists a vast number of diseases or disorders.

The specification discloses that "in the context of the present invention, the term "therapy" includes "prophylaxis" unless there are specific indications to the contrary"

(see paragraph [0019]). The present invention provides the use of a compound of formula (I), as herein described, in a method of manufacturing a medicament for the treatment or prophylaxis of thrombosis and/or hypercoagulability in blood and/or tissues; atherosclerosis; fibrotic conditions; or a condition which benefits from maintaining or enhancing bradykinin levels in the body of a mammal (such as man); for example a medicament for the treatment or prophylaxis of thrombosis and/or hypercoagulability in blood and/or tissues (see paragraph [0021]). Method of treating a condition where inhibition of carboxypeptidase U is beneficial in a mammal suffering from, or at risk of, said condition, which comprises administering to the mammal a therapeutically effective amount of a compound of formula I (see paragraph [0078]).

The specification has not provided guidance in the way of a disclosure to how to determine individuals that need protection against disorder, condition or disease, such as thrombosis or atherosclerosis. Furthermore, the specification does not disclose what the effective amount of the formulation to be administered in the treatment or prophylaxis of diseases, such as thrombosis or atherosclerosis. As described above, the Merck manual indicates that there are plethora of disorders known that are related to thrombosis, for example, arterial, cardiac, cavernous sinus, cerebral, coronary artery, deep venous and others (see Merck manual, "index entries"). Merck manual indicates that numerous genetic acquired, and environmental factors can tip the balance in favor of coagulation, leading to the pathologic formation of thrombi in veins (e.g., deep vein thrombosis [DVT]), arteries (e.g., MI, ischemic stroke), or cardiac chambers. Thrombi can obstruct blood flow at the site of formation or detach and embolize to block a distant

blood vessel (e.g., pulmonary embolism, stroke) (see Merck manual, “Thrombotic Disorders”, 1st paragraph). Further, Merck manual indicates that genetic defects increase the propensity for venous thromboembolism. However, other disorders and environmental factors can increase the risk of thrombosis, especially if present in conjunction with one of the genetic abnormalities. Stasis associated with surgery or orthopedic or paralytic immobilization; heart failure; pregnancy; and obesity increase the risk of venous thrombosis. Tissue injury from trauma or surgery exposes tissue factors to blood and increases the risk of venous thrombosis. Neoplastic cells predispose to venous thrombosis. Sepsis and other severe infections associated with increased tissue factor exposure can increase the risk of venous thrombosis. Oral contraceptives that contain estrogen increase the risk of arterial and venous thromboembolism. Atherosclerosis predispose to arterial thrombi (see Merck manual, “Thrombotic Disorders", 2nd to 8th paragraphs). Merck manual indicates that for diagnosis and treatment, predisposing factors should always be considered. In some cases, the condition is clinically obvious. If no predisposing factor is readily apparent, further evaluation should be conducted in patients with a family history of venous thrombosis (see Merck manual, "Thrombotic Disorders", 9th paragraph). The Merck manual further indicates diagnostic tests for the cause of thrombosis (see Merck manual, “Thrombotic Disorders”, 10th to 18th paragraphs).

The Merck manual indicates that Atherosclerosis is patchy intimal plaques (atheromas) in medium-sized and large arteries; the plaques contain lipids, inflammatory cells, smooth muscle cells, and connective tissue. The Merck manual

indicates that the risk factors include dyslipidemia, diabetes, cigarette smoking, family history, sedentary lifestyle, obesity, and hypertension. Diagnosis is clinical and confirmed by angiography, ultrasonograpy, or other imaging tests. Treatments include risk factor and dietary modification, physical activity, antiplatelet drugs, and antiatherogenic drugs (see Merck manual, “Atherosclerosis”, 1st paragraph). The Merck manual indicates that atherosclerotic plaques may be stable or unstable. Stable plaques regress, remain static, or grow slowly over several decades until they may cause stenosis or occlusion. Unstable plaques are vulnerable to spontaneous erosion, fissure, or rupture, causing acute thrombosis, occlusion, and infarction long before they cause stenosis. The Merck manual indicates that most clinical events result from unstable plaques, which do not appear severe on angiography (see Merck manual, "Atherosclerosis", 6th paragraph). The Merck manual indicates that there are multiple risk factors (see Merck manual, “Atherosclerosis”, “Risk Factors”). Furthermore, the Merck manual indicates that atherosclerosis is initially asymptomatic, often for decades. Symptoms and signs develop when lesions impede blood flow. Atherosclerosis may also cause sudden death without preceding stable or unstable angina pectoris (see Merck manual, “Atherosclerosis”, “Symptoms and Signs”). Additionally, the Merck manual indicates that diagnosis depends on the presence of absence of symptoms (see Merck manual, "Atherosclerosis", "Diagnosis"). Furthermore, the Merck manual indicates different treatments, such as lifestyle change, drug treatment of diagnosed risk factors, antiplatelet drugs, or possibly statins, ACE inhibitors, β-blockers, and diet changes.

There is no clear guidance as to how to determine the patient population, since not all people suffer from the same disorder, condition or disease. Since art recognizes that there are countless different conditions, disorders and diseases, but does not provide how to determine the individuals who are susceptible to the disorder, condition or disease, such as thrombosis and atherosclerosis, and does not provide guidance as to the effective amount of administration, more guidance is necessary.

(8) The quantity of experimentation necessary:

In order to treat a disease, a dosage, the subject and regimen must be identified. In order to ameliorate a disease symptoms or conditions, the end point of the treatment also needs to be identified. Since it is uncertain to predict the patient population who are susceptible for disorder, condition or disease, and the Applicant have not provided the appropriate time frame at which the compound should be administered and the effective dosage, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the compound would be effective in treating an adult, child, or an infant from all disorder, condition or disease.

Please note that the terms "prevent" and "prophylaxis" are absolute definitions that mean to stop from occurring and, thus, require a higher standard for enablement than does "therapeutic" or "treat" or "alleviate", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes)- including preventing such disorders as thrombosis or

atherosclerosis, which is clearly not recognized in the medical art as being totally preventable condition.

Rejection-35 U.S.C. 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

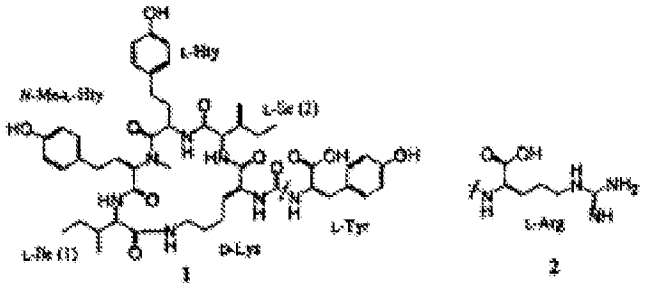
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 5-6, 16-17 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itou et al (Bioorganic & Medicinal Chemistry Letters, 1999, 9: 1243-1246, filed with IDS) in view of Bajzar (Arteriosclerosis, Thrombosis, and Vascular Biology) and Klement et al (Blood, 1999, 94: 2735-2743).

12. Itou et al teach Anabaenopeptins G and H are potent carboxypeptidase A inhibitors. Itou et al teach that the Anabaenopeptins G and H has the structures



, wherein X is $(CH_2)_4$ and R^1 is CO_2R^{15} wherein R^{15} is H. meeting the structural limitations of claims 1 and 5-6. The difference between the reference and the instant claims is that the reference does not teach Carboxypeptidase U inhibitor or the diseases or disorders being treated.

13. However, Bajzar reference teaches that thrombin activatable fibrinolysis inhibitor (TAFI) accounts for antifibrinolytic activity (see abstract. Figure 1, Figure 2). Bajzar reference teaches that TAFIa exhibits carboxypeptidase B-like specificity, which likely inhibits fibrinolysis by catalyzing the removal of C-terminal lysines of fibrin partially degraded by plasmin; TAFI and its activation by thrombin-thrombomodulin and plasmin constitute an antifibrinolytic pathway analogous to the anticoagulant protein C pathway (see p. 2516, "Conclusion").

14. Klement et al teach that bleeding is observed with increased concentrations of thrombolytics as well as with adjunctive antithrombotic and antiplatelet agents. A novel approach to enhance thrombolytic therapy is to inhibit the activated form of thrombin-activatable fibrinolysis inhibitor (TAFI), which attenuates fibrinolysis in clots formed from human plasma (see abstract). Klement further teaches that TAFIa is inhibited by a carboxypeptidase inhibitor isolated from the potato tuber (PTI), and this is a specific inhibitor of both the carboxypeptidase A and B family of proteases (see p. 2735, right column, 1st full paragraph). Klement teaches that the zymogen TAFI is found in human plasma and circulates as a precursor of exopeptidases with carboxypeptidase B-like specificity, and is also referred to as procarboxypeptidase U (see p. 2735, right column). Klement teaches that inactivation of thrombin or activated TAFI (TAFIa) during thrombolysis would improve outcome (see p. 2735, left column, 1st paragraph). Klement further teaches that PTI specifically potentiates tPA-induced fibrinolysis in clots of human plasma (see p. 2738, right column, 3rd full paragraph). Further, Klement teaches that PTI would be present and able to completely inhibit TAFI-dependent prolongation of lysis time in vivo (see p. 2739, left column, bottom). Klement teaches that PTI could be used as a TAFI inhibitor in potentiation of thrombolysis in vivo (see p. 2742, left column, 1st paragraph), and inhibitor of TAFIa, delivered systematically, is capable of potentiating tPA-induced lysis of a platelet-rich arterial thrombus (see p. 2742, left column, 2nd paragraph).

15. Therefore, it would have been obvious for one of ordinary skill in the art to combine the teachings of the prior arts, and try adding the potent inhibitors of

carboxypeptidase A to inhibit carboxypeptidase U (carboxypeptidase R, B) because Klement teaches that a carboxypeptidase inhibitor isolated from potato tuber (PTI) is a specific inhibitor of both the carboxypeptidase A and B family of proteases. One of ordinary skill in the art would be motivated to try adding the potent inhibitors of carboxypeptidase A to inhibit carboxypeptidase U, since Klement teaches that a carboxypeptidase inhibitor inhibits both carboxypeptidase A and B family of proteases. There is a reasonable expectation of success, since PTI is a specific inhibitor of both the carboxypeptidase A and U, one would expect that potent inhibitors of carboxypeptidase A would at least inhibit carboxypeptidase U similarly.

16. Furthermore, it has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR, When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007).

17. The "problem" facing those in the art was development of better thrombolytic agents or more effective adjunctive antithrombotic therapy to improve overall efficacy of coronary thrombolysis, and there were a limited number of methodologies available to do so, for example, development of thrombin-activatable fibrinolysis inhibitors. Itou et al teach the isolation of anabaenopeptins that are potent carboxypeptidase A inhibitors.

Since carboxypeptidase A is involved in thrombolysis, it would have been obvious to one of ordinary skill in the art to try adding the potent carboxypeptidase A inhibitors to inhibit carboxypeptidase U, since a inhibitor isolated from potato tuber was a specific inhibitor of both carboxypeptidase A and B. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. Thus, treating thrombosis wherein a compound of formula (I) to a warm-blooded animal is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/J. H./
Examiner, Art Unit 1654

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Primary Examiner, Art Unit 1654